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Energy Expenditure in Children after Severe Traumatic Brain Injury

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Abstract

Objective—To evaluate energy expenditure in a cohort of children with severe traumatic brain injury (TBI).

Design—A prospective observational study.

Setting—A pediatric neurotrauma center within a tertiary care institution.

Patients—Mechanically-ventilated children admitted with severe traumatic brain injury (GCS<9) with a weight greater than 10 kg were eligible for study. A subset of children was co-enrolled in a phase 3 study of early, therapeutic hypothermia. All children were treated with a comprehensive neurotrauma protocol that included sedation, neuromuscular blockade, temperature control, anti-seizure prophylaxis and a tiered-based system for treating intracranial hypertension.

Interventions—Within the first week after injury, indirect calorimetry measurements were performed daily when the patient's condition permitted.

Measurements and Main Results—Data from 13 children were analyzed (with a total of 32 assessments). Measured energy expenditure (MEE) obtained from indirect calorimetry was compared to resting energy expenditure (pREE) calculated from Harris-Benedict equation. Overall, MEE/pREE averaged 70.2 ± 3.8%. Seven measurements obtained while children were hypothermic did not differ from normothermic values (75 ± 4.5% vs. 68.9 ± 4.7% respectively, p = 0.273). Moreover, children with favorable neurologic outcome at 6 months did not differ from

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children with unfavorable outcome (76.4 ± 6% vs. 64.7 ± 4.7% for the unfavorable outcome, p = 0.13).

Conclusions—Contrary to previous work from several decades ago that suggested severe pediatric TBI is associated with a hypermetabolic response (MEE/pREE > 110%); our data suggest that contemporary neurocritical care practices may blunt such a response. Understanding the metabolic requirements of children with severe TBI is the first step in development of rational nutritional support goals that might lead to improvements in outcome.

Keywords

pediatric neurocritical care; traumatic brain injury; metabolism; energy expenditure; nutritional support

Introduction

In the United States, traumatic brain injury (TBI) is responsible for 1.4 million hospital visits, 275,000 hospitalizations, 52,000 deaths and more than $56 billion in acute care costs each year [1, 2]. TBI is the leading killer of children over the age of 1 year – accounting for 7440 yearly deaths in the most recent data from the CDC. An estimated 125,000 children are living with a TBI-related disability, with overall life-costs for those individuals estimated at $60.4 billion [3]. Despite these daunting statistics, our understanding of how to care for children with TBI is still rudimentary. For instance, in an updated version of the “Guidelines for Medical Management of Severe TBI for Infants, Children and Adolescents” published in 2012, no level 1 recommendations and only limited level 2 therapies could be recommended based on the available literature [4].

For nutritional support, there are a number of fundamental questions that remain unanswered, including (i) when nutrition should be started, (ii) what form of nutrition (enteral/parenteral) is optimal, (iii) how should glucose be administered/controlled and (iv) how much nutritional support is required. Fundamental to developing appropriate nutritional goals for children is an understanding of caloric expenditure of children with severe TBI since this information will inform many other aspects of nutritional support. Information from several decades ago suggested that TBI induced a “hypermetabolic state” in both children and adults, with several small studies suggesting that victims of TBI burn from 130 – 180% of estimated energy expenditure from various normative formulas [5–10]. Despite the importance of these seminal reports, the metabolic needs of infants and children after severe TBI remain unclear particularly given the fact that treatment has evolved over the past decade and has been influenced by published guidelines [4, 5]. Guidelines based therapies such as sedation, barbiturates, neuromuscular blockade (NMB), and aggressive prevention of fever and/or controlled hypothermia, among others could greatly influence metabolic demands in contemporary care. Moreover, institution of enteral feeds may also affect the metabolic demands as the gastrointestinal blood flow and metabolism would be affected [10–15].

Therefore, in order to begin to develop rationale nutritional goals, we performed a prospective, observational study to determine metabolic demands of children with severe

TBI as managed by the current TBI guidelines. Consistent with the previous literature, we hypothesized that measured energy expenditure (MEE) from indirect calorimetry would be increased above predicted values based on weight, height and sex over time after TBI. We performed these analyses when these assessments were possible over the first 7 days after TBI.

Methods

Patient Selection and Treatment Protocol

This study was approved by the University of Pittsburgh Institutional Review Board. All children less than 18 years of age admitted with severe TBI to the Pediatric Intensive Care Unit (PICU) at Children's Hospital of Pittsburgh were eligible for enrollment (Figure 1). A subset of children was concurrently enrolled in a Phase III trial of early, moderate hypothermia as a neuroprotectant (Pediatric Traumatic Brain Injury Consortium: Hypothermia or the "Cool Kids Trial"), which also allowed us to explore the impact of therapeutic hypothermia on metabolic demands in pediatric TBI [16].

All children were treated with a comprehensive protocol for the management of severe TBI that is based on published guidelines and our protocol has been previously reported [17]. In brief, children were resuscitated based on Advanced Trauma Life Support guidelines in our Level 1 trauma center that included early stabilization of the airway, institution of mechanical ventilation to ensure adequate ventilation and oxygenation and sufficient circulatory support to treat shock and ensure adequate perfusion of end organs. Comprehensive assessments were made by our trauma team to identify all injuries and an assessment of mental status was performed to determine that Glasgow Coma Scale (GCS) score. After radiological and laboratory assessments were performed, the child was taken for operative intervention or the PICU for definitive care. A comprehensive protocol for all patients who were found to have severe TBI (GCS < 9) was instituted that includes a tiered-approach to intracranial hypertension management. Within the first-tier, all children received continuous CSF diversion via an externalized ventricular drain, positional maneuvers (head of bed to 30°, neck in midline), mild hyperventilation ($PaCO_2$ ~ 35 mm Hg), sedation (predominantly using narcotics [fentanyl] exclusively) and NMB (using vecuronium). During intracranial hypertension episodes, hyperosmolar therapies (mannitol and/or hypertonic (3%) saline) and pentobarbital were administered at the discretion of the clinical team as were decisions regarding surgical approaches to mitigate such crises. Fevers (as well as intracranial hypertension) were vigorously treated.

For metabolic support, all children received isotonic, non-glucose containing fluids for the first 48 hours after admission, as previously described [18]. If serum glucose concentrations decreased below 70 mg/dL, then glucose-containing solutions were begun. Parenteral nutrition (consisting of a trophamine-based preparation for amino acids and 20% intralipids) was begun after 48 hours of hospitalization. No child received other fluids that might provide metabolic support (for example, propofol, albumin, others). Enteral feeds were started when possible after 48 hours. Nutrition, in this patient population, was not titrated based on MEE measurements.

Measurements and Data Collection

Intermittent measurements of energy expenditure (MEE) were obtained using indirect calorimetry starting at 24 hours of admission then daily afterwards until extubation or 7 days post admission. Specifically, measurements of oxygen consumption ($V\dot{O}_2$), carbon dioxide production ($V\dot{C}O_2$) and respiratory quotient were determined by direct measurement of gas exchange at the inspiratory and expiratory port of the ventilator (Ultima CPX, Medgraphics, St. Paul, Minnesota) for a period of 30 minutes. If air leak from the tracheal tube accounted for > 5% of total tidal volume or > 12% coefficient of variation was noted during the examination, then the test was deemed invalid and the results discarded. Due to equipment requirements, measurements were done when the inspired oxygen pressure (FiO_2) was less than 0.60 and inspired tidal volumes were greater than 100 ml/breath. Moreover, children were not tested unless the child had stable hemodynamics and respiratory settings for at least 2 hours, have not received any sedation or stimulation including, but not limited to endotracheal tube suctioning for at least 1 hour. In addition, steady state was determined by five consecutive minutes in which $V\dot{O}_2$ and $V\dot{C}O_2$ variations are less than 10%. No filtering was applied to the minute-to-minute data after the study was started. Instead, the entire test was cancelled and restarted if outliers were noted in the measurement.

MEE was compared to predicted Resting Energy Expenditure (pREE) based on the Harris/Benedict equation; Male: [66 + (13.7 × weight (kg)) + (5 × height (cm)) – (6.76 × age (y))], Female: [655 + (9.6 × weight (kg)) + (1.8 × height (cm)) – (4.7 × age (y))][19]. In addition, MEE was compared to pREE based on the Schofield equation; males < 3 years: [(0.167 × weight (kg)) + (1517.4 × height (m)) – 617.6], males 3 – 10 years: [(19.59 × weight (kg)) + (130.3 × height (m)) + 414.9], males 10 – 18 years: [(16.25 × weight (kg)) + (137.2 × height (m)) + 515.5], females < 3 years: [(16.252 × weight (kg)) + (1023.2 × height (m)) – 413.5], females 3 – 10 years: [(16.969 × weight (kg)) + (161.8 × height (m)) + 371.2], and females 10 – 18 years: [(8.365 × weight (kg)) + (465 × height (m)) + 200]

The data were dichotomized into two groups, with favorable neurologic outcome defined as Glasgow outcome scale (GOS) score > 3 at 6 months (as assessed either by a neuropsychologist or by chart review). Data between groups were compared using the Student's T-test. Data are presented as mean ± SEM, unless otherwise noted.

Results

Metabolic measurements were obtained on a total of 13 patients (32 overall MEE assessments, 59 other potential measurements not performed due to escalation in respiratory setting particularly FiO_2). Eight were male, aged 9.8 y ± 1.4 and weighing 42.9 kg ± 7.9. Only 3 children had associated injuries, with two suffering fractured bones and one suffering solid organ injuries. Mechanisms of injury varied widely and 5 required cranial surgery. Five children were included in a Phase III hypothermia trial, which included reducing rectal temperature to 32 – 33°C for 48 h followed by slow re-warming [16]. Overall mortality was 23% with 54% of subjects exhibiting favorable outcome.

A summary of patient demographics is presented in Table 1 and the conditions present upon testing are presented in Table 2. Of note, all but two measurements were done with the

children receiving only parenteral nutrition, and all but 3 of the evaluations were performed while the children were receiving NMB. All children underwent continuous EEG monitoring and no episodes of status epilepticus were noted at the time of metabolic assessment. Overall, MEE was 70.2 ± 3.8% of pREE for all subjects and only 5 of the MEE values were greater than expected from the Harris/Benedict equation. When MEE was compared to pREE as determined by the Schofield equation, the mean was 69 ± 4.5%, with only 3 measurements greater than expected by this equation. Seven measurements were performed when the children's rectal temperature was in the hypothermic range (32 – 34°C) and these measurements were not different from those measured during normothermia (75.0 ± 4.5% vs. 68.9 ± 4.7%, $p = 0.273$). Two measurements were done when the temperature was 38°C, but none of the measurements were done while the children were febrile.

On average, mean MEE was less than 100% predicted for each of the study days (see Table 3). Mean respiratory quotients were greater than 0.9 for the all study days except on day 2 and day 6, indicating a trend toward carbohydrate-based respiration at the time of assessments. When stratified based on outcomes, 15 measurements were done on children who ultimately demonstrated favorable outcome. Mean MEE/pREE in the favorable outcome group was 76.4 ± 6% vs. 64.7 ± 4.7% in the unfavorable outcome group, but this difference did not reach statistical significance ($p = 0.13$) (Figure 2).

Discussion

Our findings strongly suggest that contemporary neurocritical care – as evidenced within our standardized protocol of sedation, NMB, temperature control, anti-seizure prophylaxis parenteral nutrition support among other factors – largely blunts the potential hypermetabolic response to TBI in children. These results suggest caloric expenditures are approximately 70% of estimated needs based on standard formulas in our center. In our limited sample, there did not seem to be an identifiable effect over time or in subjects with favorable/unfavorable outcomes. These results may have implications for nutritional goals for children with severe TBI. Our findings contrast with results from the adult TBI victims, which have found a profound hypermetabolic response of 130 – 180% of estimated energy expenditures [10, 20–23]. On the other hand, a recently published article by Osuka and colleagues [24] has demonstrated a lower MEE than predicted by Harris – Benedict equation in 10 patients treated with controlled normothermia, sedation and NMB.

There are 3 studies including children that have largely shaped the literature with regard to metabolic demands after severe TBI. All of those studies compared MEE to predicted REE as estimated by the Harris – Benedict equation, despite the inaccuracy of this equation in predicting metabolic needs of critically ill children [25–27]. Moore and colleagues [9] studied a series across the age range, of which 9 were children with severe TBI (range 3 – 22 years). MEE/pREE for these children was 112 – 255%, and RQ range was 0.42 – 1. On closer scrutiny, 3 of these children had minor associated injuries - kidney laceration, splenic laceration and clavicular fracture – similar to children within our study. Methodologically, MEE was calculated over a 10-minute period of time (in contrast to our more prolonged assessment) and the timing of assessments was not specified. Moreover, the authors did not report on the type of sedation provided to the children or whether neuromuscular blocking

agents were administered. In addition, mean temperature was reported to be 38.2°C ± 0.3, but the temperature at the time the study was conducted was not reported. There are several variables that could explain the differences of results between the two studies. Phillips and colleagues [8] reported on MEE from 9 children between 2 and 17 years of age after severe TBI. In this population, 7 children suffered multi-trauma along with severe TBI, 1 child received NMB and 1 required pentobarbital and sedation practices were not described. Phenytoin was only used in case of seizures and antipyretics were used to control temperature. Seven children received parenteral nutrition and 5 received enteral nutrition, yet they did not report the mode of nutrition at the time of the assessment – which might impact the variation observed in their findings (94 – 176% of pREE). Lastly, Matthews and colleagues [7] reported data from 18 children between 2 and 15 years of age. In their clinical protocol, all children were received narcotics, benzodiazepines and NMB. In the 105 assessments, MEE/pREE was within (i) the normal range (85 – 115%) for 82% of measurements, (ii) above normal (> 115%) for 4% of the measurements and (iii) below normal (< 85%) for 14% of the measurements. However, almost two thirds of these low values were observed in two children who died early after injury. By comparison, we found 28% within the normal range and the remaining 72% below normal. They found no difference in MEE/pREE between patients receiving enteral (98.7%) and parenteral (96%) nutritional support. Methodologically, there are several differences with our study – particularly, as they included children with uncuffed tracheal tubes (which may lead to inaccuracies of $V\dot{C}O_2$ determination) and body temperatures were not recorded.

It is difficult to fully evaluate energy expenditure goals after TBI because of the interconnected nature of this process with other clinical concerns. Sedatives and barbiturates are reported to decrease metabolism by 13 – 32% [10, 11, 13, 14] and NMB by 10 – 28% [10, 14, 28–31]. Although the route/type of feeding are believed to influence energy expenditure [32, 33], some studies have failed to show this relationship [23, 29, 33, 34]. For instance, Borzotta and colleagues found no difference in metabolism between different nutrition strategies when measured [34], while McCall and colleagues found a 10% difference between groups [29]. Bruder and colleagues suggested that temperature variations could contribute for all the variations noted in metabolism due to differences in sedation, NMB or barbiturates [12], while Clifton and colleagues reported increases in MEE that far exceed what could be explained by increased temperature alone [10].

There are several implications from our data. As stated earlier, evidence regarding nutritional support after severe TBI in children is scant. While a randomized-controlled trial testing the effectiveness of an immune-enhanced diet [35] was performed and failed, there is little other evidence to guide clinicians. Our data suggest that we have more fundamental questions to answer before novel trials can advance the field. In a recent paper, we found that the nutritional goals among 32 international TBI centers vary substantially – ranging from sites that provide nutritional support immediately after injury to those who delay feedings for many days [36]. Based on the data regarding MEE/pREE from several decades ago, a reasonable strategy might be to start caloric replacement early and at supra-normal levels to keep pace with this presumed hypermetabolism. However, suggest that this approach might lead to over-feeding and the potential for adverse effects – such as an

increase in carbon dioxide production that might hinder respiratory and CNS care and potential toxicities/complications from parenteral or enteral nutrition [37–41]. On the other hand, inadequate nutritional support may depress immune system function, delay wound healing and lead to respiratory muscle weakness. In our institution, we have chosen to measure caloric requirements and try to meet this goal for each child until further evidence is can guide an optimal approach.

We were surprised that therapeutic hypothermia did not produce a measureable effect of MEE in our patients, although our sample size was quite small for this subgroup. Tokutomi and colleagues reported a highly significant reduction (approximately 30%) in energy expenditure between 37°C and 32°C in 15 adults with severe TBI [42]. However, the baseline values in these patients were ~130–140% of predicted based on the Harris-Benedict equation which could represent a greater target for hypothermia to affect than in our series. Only 13% of those patients had a favorable recovery in contrast to the 53% of our patients. It is also noteworthy that only 3 of the 13 patients in our study were being treated with barbiturates during the MEE assessments. That fact makes it difficult to reconcile our findings of low MEE as simply being a function of deep sedation—although the impact of all of the various sedatives, analgesics, and NMB on MEE in comatose children remains to be fully defined.

Our study has several limitations. Our sample size is not large enough to make conclusive recommendations for all children with severe TBI. In addition, our data are concentrated predominantly in the early period after TBI, and data in delayed time periods might be different. We chose to compare our findings with indirect calorimetry to the Harris/Benedict equation, and other formulas could have been chosen. However, the Harris/Benedict equation has been the main equation used in other studies to estimate metabolic demands. We recognize that the approach to nutritional support greatly influences MEE and two factors could be important in this regard with regard to generalizability of the finding. First, nearly all of the measurements were made in children being administered parenteral nutrition – thereby minimizing any effect that enteral feeds might have on energy expenditure. Second, as indicated, we generally withhold glucose in the initial 48 hours after injury while closely monitoring blood glucose concentration [18]. In the survey referenced earlier [36], this approach is taken at ~ 30% of pediatric TBI centers likely given the long-recognized concerns in animal models and patients regarding hyperglycemia in the injured brain [43, 44]. However, we also recognize that the impact of withholding glucose on MEE in children with severe TBI remains to be determined. Thus, our approach to nutrition, although Guidelines based [4] could importantly influence the findings relative to what might be seen in other centers. Lastly, our patient population was treated with a rigorous protocol that has been evolved over the years to reflect our beliefs in the best therapies for these children. Our protocol is consistent with the currently published guidelines, but other centers may choose other strategies related to sedation, NMB or any number of other factors. These other factors may affect the MEE/pREE in other centers.

In conclusion, our data contradict previous work that suggested that children with severe TBI are hypermetabolic and the inference that this finding suggested that clinicians should aggressively achieve supra-normal caloric goals for such children. Our data suggest that

contemporary neurocritical care may largely blunt this response, and most of our readings suggested that children consumed fewer calories than published formulas might suggest. We consider this a first step in understanding how to optimally deliver nutrition to children with severe TBI and believe that larger studies across many institutions will be required to ultimately answer the substantive question – how should we provide nutritional support to children with severe TBI to optimize their outcome and recovery.

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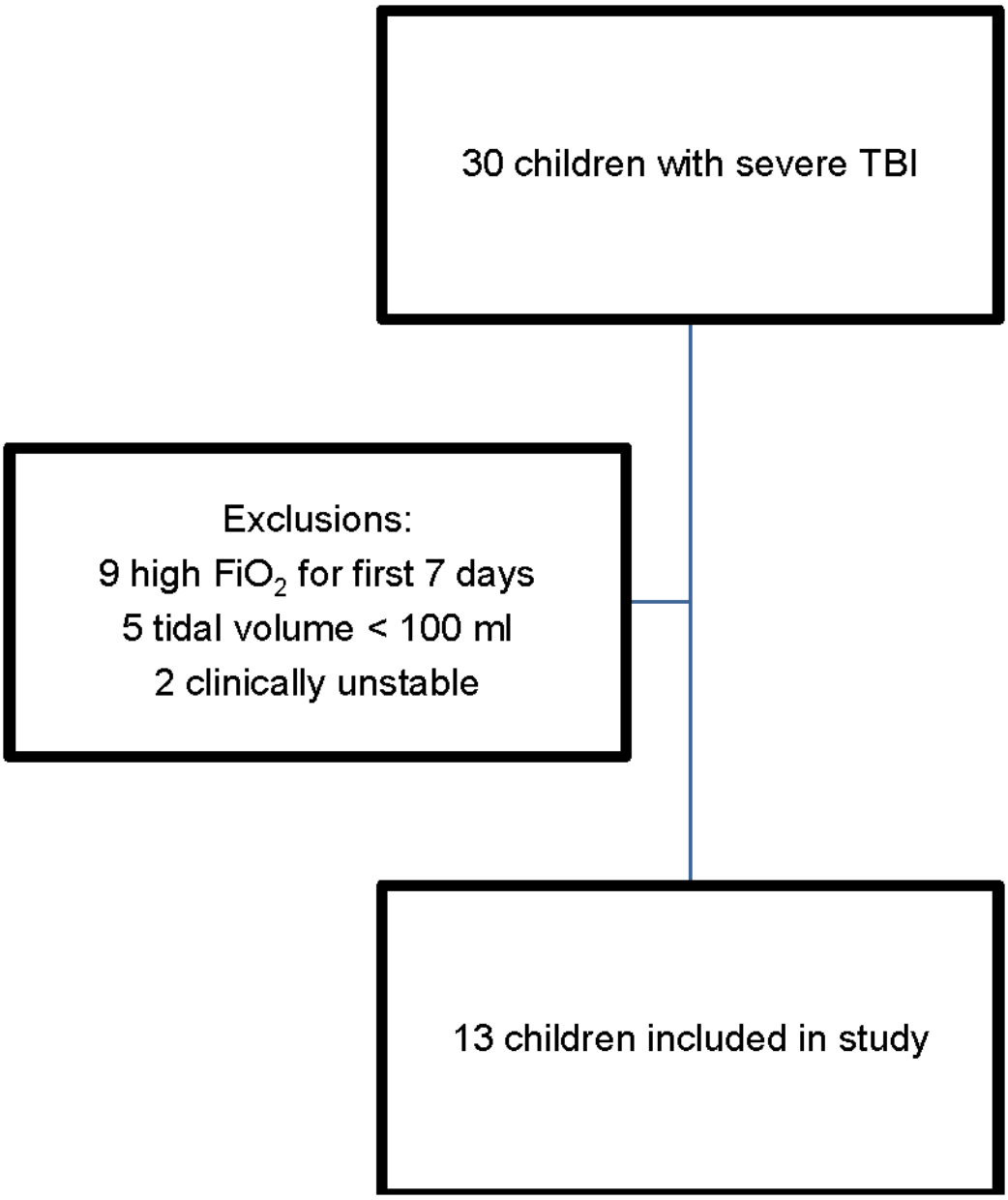

Figure 1.
Patient flow diagram indicating number of children screened, excluded and included in study

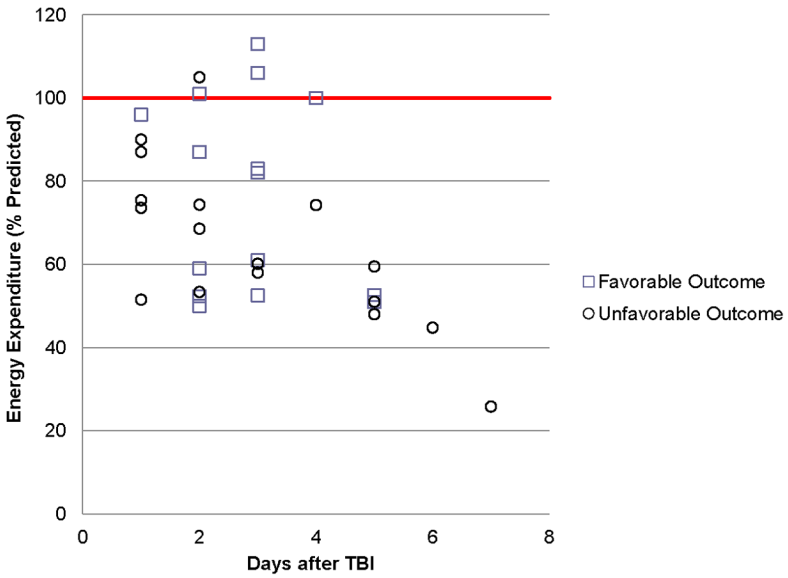

Figure 2.

The relationship between measured energy expenditure/predicted resting energy expenditure (based on the Harris/Benedict equation, MEE/pREE) over time in children who ultimately had favorable (□, GOS < 3 at 6 mo) and unfavorable (○, GOS ≥ 3 at 6 mo) outcomes.

Table 1

Patient demographics.

Age (y)	Gender	Weight (kg)	Height (cm)	Mechanism of injury	Intracranial findings	Cranial Surgery?	Associated injuries	ISS	GCS	GOS
2	Female	9.3	74.3	Fall	Subdural hematoma	Yes	None	21	3	1
1.8	Male	10.4	80	Fall	Subdural hematoma	Yes	None	30	6	2
2	Male	10.7	86.4	AHT	Subdural hematoma	No	None	26	8	3
13.6	Male	36	145	Blunt	Hemorrhagic contusions	Yes	None	34	6	1
14.6	Male	73.4	158	Dirt bike	Parenchymal and ventricular hemorrhage	No	None	10	8	4
10.8	Female	50.4	148	Gunshot	Intraparenchymal hemorrhages	Yes	None	26	3	4
11.5	Female	30.7	144	Car vs. Ped	Intraparenchymal hemorrhages	No	None	21	6	5
6.9	Male	17	116	Fall	Intraparenchymal hemorrhage	No	None	25	7	5
14	Female	90	165	Bicycle fall	Subdural and subarachnoid bleed	Yes	None	34	3	1
11	Male	50	152	ATV	Intraparenchymal hemorrhage	No	Femur fracture	31	6	5
9	Male	40	136	Bicycle fall	Diffuse edema	No	None	26	6	2
14	Male	90	180	ATV	Cerebral edema	No	Clavicle and spine T2 fracture	24	7	5
16	Female	50	167	MVC	Diffuse axonal injury	No	Lung contusion, splenic laceration, pelvic fracture	29	5	5

ISS-Injury Severity Score, GCS-Glasgow Coma Score on admission, GOS: Glasgow Outcome Score at 6 months, Ped: Pedestrian

Table 2

Variables at time of indirect calorimetry measurement of energy expenditure (MEE).

	MEE/pREE$_{HB}$	MEE/pREE$_{S}$	REE	Temperature	ICP	Barbiturates	NMB	Mode of nutrition
1	87	153	82	32.5	49	Yes	Yes	P
2	52	52	30	36.0	12	No	Yes	P and E
	74	74	42	38.0	9	No	Yes	E
	69	69	39	37.0	8	No	No	E
	53	53	31	37.8	6	No	No	E
3	59	55	35	37.7	4	No	Yes	P
	45	41	26	37.3	13	No	Yes	P
	26	24	15	38.0	1	No	No	P
4	90	83	30	36.4	8	No	Yes	P
	105	97	35	37.0	18	No	Yes	P
	48	44	16	36.9	16	Yes	Yes	P
	51	47	17	37.2	8	Yes	Yes	P
5	83	68	18	33.0	10	No	Yes	P
6	52	57	15	37.7	9	No	Yes	P
	50	54	14	36.5	10	No	Yes	P
7	82	91	33	37.3	10	No	Yes	P and E
8	59	53	28	34.3	17	No	Yes	P
	53	48	25	37.3	3	No	Yes	P
	53	48	25	36.7	14	No	Yes	P
	51	46	24	37.2	20	No	Yes	P
9	58	59	11	33.2	19	Yes	Yes	P
10	101	94	29	37.2	15	No	Yes	P
	106	100	31	37.2	8	No	Yes	P
	113	106	33	37.0	3	No	Yes	P
	100	94	29	37.0	2	No	Yes	P
11	75	71	24	32.4	3	No	Yes	P

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	MEE/pREE$_{HB}$	MEE/pREE$_{S}$	REE	Temperature	ICP	Barbiturates	NMB	Mode of nutrition
	74	70	24	32.4	8	No	Yes	P
	60	57	19	35.6	7	No	Yes	P
	74	70	24	35.0	2	No	Yes	P
12	87	79	19	32.5	7	No	Yes	P
	61	55	14	32.9	8	No	Yes	P
13	96	94	26	37.8	4	No	Yes	P

MEE/pREE$_{HB}$ - Measured energy expenditure/ predicted resting energy expenditure by Harris – Benedict equation, expressed as percentage; MEE/pREES - Measured energy expenditure/ predicted resting energy expenditure by Schofield equation, expressed as percentage; REE – Resting Energy Expenditure expressed as Kcal/kg/day; ICP - intracranial pressure; NMB - Neuromuscular Blockade; Mode of nutrition - Parenteral (P), Enteral (E)

Table 3

Daily metabolic measurements over time (mean ± SEM)

	Day 1 N= 6	**Day 2 N= 9**	**Day 3 N= 8**	**Day 4 N= 2**	**Day 5 N= 5**	**Day 6 N= 1**	**Day 7 N= 1**
MEE/pREE	79 ± 6.5%	72.3 ± 7%	77.0 ± 8.1%	87.1 ± 12.9%	52.4 ± 1.9%	44.8%	25.8%
RQ	0.90 ± 0.098	0.83 ± 0.04	1.00 ± 0.11	0.96 ± 0.16	0.98 ± 0.04	0.74	1
$V\dot{O}_2$	116 ± 23.16	129.22 ± 23.9	155.38 ± 20.75	168 ± 39	66.6 ± 6.4	41	23
$V\dot{C}O_2$	96 ± 17.3	103.22 ± 18.49	148.25 ± 18.57	154 ± 12	65 ± 6.86	31	22

$V\dot{O}_2$and $V\dot{C}O_2$ expressed in ml/min